REMARKS

Claims 28, 30-33, 36-40, 43-44 and 47 are currently pending. Claims 28, 30-33, 36-40, 43-44 and 47 stand rejected under 35 USC §103(a) as allegedly being unpatentable over Ohnishi, *et al.*, J. Hum. Genet., Vol 46, pages 471-477 (hereinafter "Ohnishi"), in view of the Cystic Fibrosis Mutation Database (hereafter CFMDB) and Fors et al., 2000, Pharma. 1:219-229 (hereafter Fors), Mein *et al.*, Genome Research, vol 10, pages 330-343, 2000 (hereinafter "Mein") and Hall et al., 2000, Proc. Natl. Acad. Sci. 97:8272-8277 (hereafter Hall).

For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, independent Claims 28, 37, and 44 are herein amended to recite that the number of PCR cycles is 17 or fewer cycles. Claims 31-32 and 39-40 are cancelled in view of this amendment.

The Examiner asserts that an ordinary artisan would have been motivated to have used 17 cycles or fewer to avoid the well known difficulties of PCR amplification taught by Hall. As noted by the Examiner, exponential amplification introduces possibilities of amplicon cross contamination. The Examiner further asserts that " it is not inventive to discover the optimum or workable ranges by routine experimentation". However, Hall teaches the complete avoidance of amplification cycles, *i.e.*, zero cycles. Thus, the use of *any* PCR cycles, even the limited number of cycles taught in the instant application, does not fall within the "optimum or workable ranges" taught by Hall.

As noted by the Examiner, Ohnishi teaches the feasibility of undertaking genome-wide association studies using blood samples of only 5-10 ml. Ohnishi makes a particular point that such studies require large amounts of DNA (abstract), and Ohnishi teaches the use of *35 cycles* of amplification to in order to reduce the amount of genomic DNA needed for genotyping, even when amplification is followed by Invader assay detection. As stated by Ohnishi, "The greatest advantage of the system described here is the significant reduction in the amount of genomic DNA required for genotyping . . ." (Discussion, page 474). Similarly, Mein teaches the use of 35 cycles of PCR to reduce the amount of genomic DNA needed for typing using the Invader assay.

The Examiner fails to acknowledge that the number of cycles is directly linked to the advantages of PCR as taught by Ohnishi and Mein, and that reduction in the number of cycles is contrary to the objectives of both Ohnishi and Mein. The difference in the amount of DNA

produced by PCR at different numbers of cycles is especially striking when one considers that the amount of detectable product essentially doubles with each cycle, as shown below:

PCR Cycles	Yield of target copies	Fraction compared to 35 cycle yield
1	2	
2	4	
3	8	
4	16	
5	32	
6	64	
7	128	
8	256	
9	512	
10	1,024	
11	2,048	
12	4,096	
13	8,192	
14	16,384	
15	32,768	
16	65,536	
17	**131,072**	**1,048,576**
18	262,144	
19	524,288	
20	**1,048,576**	**131,072**
21	2,097,152	
22	4,194,304	
23	8,388,608	
24	16,777,216	
25	**33,554,432**	**4,096**
26	67,108,864	
27	134,217,728	
28	268,435,456	
29	536,870,912	
30	**1,073,741,824**	**128**
31	2,147,483,648	
32	4,294,967,296	
33	8,589,934,592	
34	17,179,869,184	
35	**34,359,738,368**	**1**

Assuming 100% yield per cycle (perfect doubling); a PCR run for only 17 cycles produces less that 1 millionth as many target molecules than a reaction run for 35 cycles. Even if PCR is imperfect, *e.g.*, is only 98% efficient, 17 cycles produces only about 110,500 copies of target, compared to about 24.2 billion copies produced in 35 cycles. Given that both Ohnishi and Mein have stated objectives of producing large amounts of amplified target DNA for genotyping, one of skill in the art would not reasonably consider a million-fold reduction, or even a 220,000-fold reduction of the desired product to be within the "optimum or workable ranges" of the methods taught by these references. Rather, limiting the number of cycles according to the instant claims is directly *contrary* to the teachings of these references.

In summary, Hall teaches against the use of *any* PCR, while Ohnishi and Mein teach that 35 cycles should be used to produce large amounts of DNA for multiplex genotyping. The references themselves have conflicting objectives with respect to PCR, and they teach away from making the combination proposed by the Examiner.

For the reasons recited above, Applicants respectfully submit that the combination of Ohnishi, Hall and Mein fails to establish obviousness of the embodiment of the invention as presently claimed. Applicants therefore respectfully request that these rejections be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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